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22 January 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 2004D-0462

Dear Dr. Silverman and the FDA Guidance Panel:

As an academic physician with an interest in oxygen therapeutic research, I would like to take this opportunity to congratulate your Panel on a comprehensive guidance document for industry regarding "Criteria for safety and efficacy evaluation of oxygen therapeutics as red blood cell substitutes." While I have prior experience with clinical trials of Oxygent™ and Hemolink™, I am not currently involved in any ongoing trials of oxygen therapeutics nor do I currently have any financial relationship with pharmaceutical companies in this field. However, because I consider research in this field essential to the future of transfusion medicine as well as care of the complex surgical patient, I would like to offer comments on the draft guidance under consideration (Docket #2004D-0462). While I concur with the vast majority of the document, I would like to address certain statements as follows:

Section III C

Although red cell transfusion has been considered standard of care for patients with massive blood loss or inadequate tissue oxygen delivery due to anemia, the true risk of red blood cell transfusion is unknown. Outcome studies of critically ill patients receiving transfusions (Hebert PC et al, N Engl J Med 340:409-17, 1999; Vincent JL et al, JAMA 288:1499-1507, 2002) suggest that transfusion therapy carries additional unspecified risks that contribute to adverse outcome, leaving our understanding of the "interaction of these agents with various clinical states" rudimentary for red blood cells as well as for oxygen therapeutic agents. The statement that, "we do not consider these surrogate endpoints to be acceptable as measures of the effects of hemoglobin- and perfluorochemical-based red cell substitutes," seems to imply that surrogate endpoints, while acceptable for evaluation of red blood cell transfusion, would not be important for oxygen therapeutic agents. In my opinion, evidence of increased tissue oxygen consumption, improved regional microcirculatory blood flow, or improvement in markers of end-organ dysfunction would represent surrogate endpoints of great value in the evaluation of an oxygen therapeutic agent. Development of an agent that effectively reduces allogeneic red blood cell transfusion without major toxicity would also be beneficial, especially in certain subgroups of patients. I would recommend deletion of the second paragraph of this section.

Durham, North Carolina 27710

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Section III C, 2. Perioperative Indications:

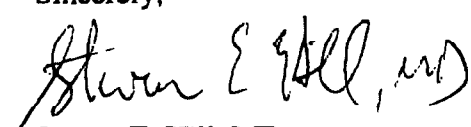
I agree that an oxygen therapeutic agent that is safe in euvolemic, anemic patients may not be safe in hypovolemic or unstable patients. However, I disagree that a large trial proving efficacy and safety in trauma is necessary for complete evaluation of an oxygen therapeutic agent in an elective surgical patient population. Given the lack of control over outcome by investigators in the trauma setting, requiring evaluation of the agent in a trauma setting may postpone or eliminate the possibility of approval for agents that are well studied in the non-trauma setting and prove to be beneficial for the patient. As long as trials in the elective surgical setting involve patients with significant blood loss, such as high blood loss orthopedic or urologic procedures and are adequately powered to support efficacy, inclusion of adequate numbers of patients in the trial that become "unstable" should allow evaluation of critical endpoints for safety. While I understand the desire for proof of an effective agent for use in trauma patients, I am concerned about bias toward approval only for an agent useful in trauma. I am also concerned that efficacy and safety in trauma may prove impractical and inconclusive.

Section IV B, 2. Elective Surgery:

For the same reasons that I object to the recommendation of study in a trauma trial as necessary for adequate evaluation in a perioperative setting, I am concerned about guidance that recommends that "the enrolled study population also reflects the characteristics of the general surgical population." It is distinctly possible that an oxygen therapeutic agent may prove safe and efficacious in high-blood-loss orthopedic or urologic surgery. If the study population does not mirror the general surgical population (such as the populations undergoing prostatectomy or scoliosis surgery) but the oxygen therapeutic agent proves both safe and efficacious in a large phase III trial, I would hope that the agent would still be seriously considered for approval with limitations.

I greatly appreciate the opportunity to comment on the draft guidance. Progress in oxygen therapeutic research promises to supplement our strained blood supply and provide an alternative to the risks of allogeneic red blood cell transfusion. Achievement of these goals will ultimately improve patient care. Thank you for taking my suggestions into consideration.

Sincerely,



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